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Familial Mediterranean Fever in Two Bedouin Families: Mutation Analysis and Disease Severity

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Familial Mediterranean fever (FMF) is an autosomal recessive disease prevalent among non-Ashkenazi Jews, Armenians, Arabs, and Turks. The Bedouin are nomad Arab tribes residing in desert margins of the Middle East and Arabia. FMF is quite rare in Bedouins, and here we report on two Bedouin families from southern Israel suffering from this disorder. The *MEFV* mutations found in the Bedouin patients M694I, V726A, and E148Q are consistent with their Arab origin. The disease severity score showed a mild to moderate severity disease in six patients. The Bedouins, leading a unique nomadic life, may prove instrumental in unraveling the role of environmental factors in the course and severity of FMF. Am. J. Med. Genet. 92:247–249, 2000.

KEY WORDS: Bedouins; FMF; *MEFV*; mutation analysis

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and polyserositis. It affects primarily people of Mediterranean origin, mostly non-Ashkenazi Jews, Armenians, Arabs, and Turks [Barakat et al., 1986; Ozdemir and Sokmen, 1969; Schwabe and Peters, 1974; Sohar et al., 1967]. It also has been found in other ethnic groups such as Anglo-Saxons and Germans [Stanbury et al., 1978]. The disease is characterized mainly by fever with abdominal pain and/or arthritis, episodes of pleuritis, erysipelas-like disease, orchitis, and pericarditis [Livneh et al., 1996]. The clinical features and severity of the disease varies among different ethnic groups; for instance, Iraqi Jews have less severe disease with fewer episodes of arthritis and erysipelas-like erythema compared with non-Ashkenazi Jews [Pras et al., 1998]. The gene responsible for the disease (*MEFV*) has been identified recently [French Consortium, 1997; International FMF Consortium, 1997]. So far, 16 mutations have been associated with FMF; the 3 common mutations are M694V, V726A, and E148Q [Booth et al., 1998; International FMF Consortium, 1997].

Bedouins are nomadic tribes, most of whom reside in the southern part of Israel (the Negev). They comprise 18% of the population of the Negev, approximately 100,000. To the best of our knowledge, FMF has not been described in Bedouins. Recently we had the opportunity to treat two families of Bedouins with this disease. The aim of this study was to perform a mutation analysis and determine the clinical correlates of the mutations in these Bedouin families.

MATERIALS AND METHODS

Patients

Blood samples were obtained from 18 individuals, including 6 FMF patients recruited from two Bedouin families. Patients were diagnosed with FMF according to published clinical criteria [Livneh et al., 1997]. The FMF patients are regularly followed at the Pediatric and Adult Rheumatic Disease Units at the Soroka Medical Center. This hospital serves as a tertiary care referral center for the Negev desert region.

Scoring of Disease Severity

The severity of the disease, reflecting the degree of patient suffering and/or the extensiveness of the disease, was determined using a modification of the disease severity score by Pras [1997].

Detection of Mutations in the Pyrin Gene

DNA was prepared from 200 μL of peripheral blood samples using a commercial kit (Nucleon BACC2, Amersham, U.K.). Mutations M680I, M694V, and V726A were screened using a commercial kit (Pronto FMF Gamidagen, Ill.). Mutation 744 was screened using an ARMS assay, as published [Bernot et al., 1998]. Other

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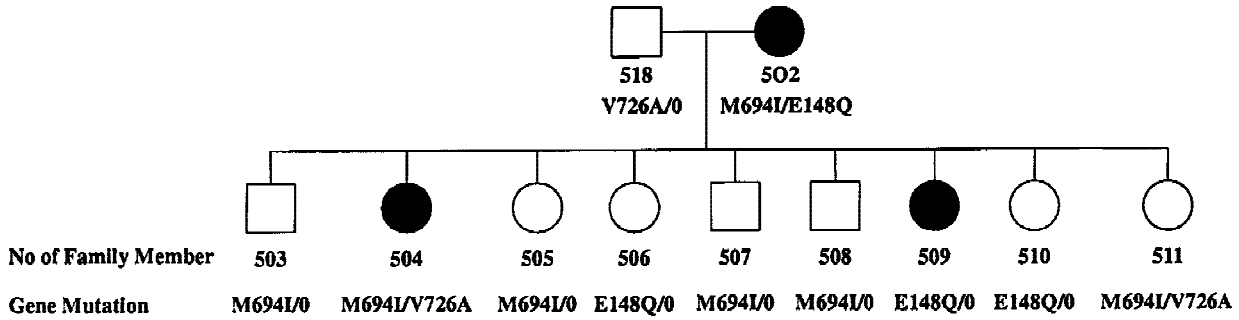

Fig. 1. Distribution of *MEFV* mutations in family 2.

mutations in exon 10 were screened by nucleotide sequencing from position 2075 through 2364, using the 5′ primer CATCCATAAGCAGGAAAGGG and the 3′ primer GGCCCCTGACCACCCACTGG (Thermosequenase, Amersham, U.K.). Mutation E148Q in exon 2 was detected by enzymatic restriction of a BstN1 site generated by the mutation, following polymerase chain reaction amplification of a 150-bp fragment [Livneh et al., 1999]. Cut and uncut fragments were resoluted on precasted 4–20% acrylamide gradient gels (Novex USA). A complete sequence of the *MEFV* coding region was performed on DNA samples of two patients (patients 509 and 501, Fig. 1) using an automated DNA sequensor at the Arthritis and Rheumatism Laboratory at the National Institutes of Health.

RESULTS

The *MEFV* mutations in the first Bedouin family are shown in Fig. 2. The mother is a carrier of mutation V726A, and the three children with FMF are compound heterozygotes for mutations M694I and V726A. Two of the healthy children are carriers of mutation M694I. The father's DNA was not available. The severity score for the patients of this family (patients 513, 516, and 517) is shown in Table I. Their total scores reached 7, 3, and 5, respectively, indicating a moderate disease in two patients and mild disease in one patient.

In family 2, the mother and two of her children have FMF (Fig. 1). The mutation analysis revealed that the mother is compound heterozygous for mutations M6941 and E148Q. The healthy father carries mutation V726A. One sick child (504) is compound heterozygous for mutations M694I and V726A. All other children, including the sick child, 509, were found to be carriers of one maternal mutation. The exception is a 4-year-old child (511) who has no clinical symptoms of FMF but carries the gentoype M6941/V726A. Sequencing of the complete coding region of *MEFV* from the child with FMF and one identified mutation (509) revealed no additional mutations. Thus, putative novel mutations were not detected in this patient. The severity scoring for patients in family 2 is presented in Table I. The score reached 3 for the mother and 5 and 3 for the sick children (504, 509, respectively).

DISCUSSION

Bedouins are nomad tribes living in the southern part of Israel and in neighboring countries in North Africa and the Arabian Peninsula. They practice Islam, but are thought to be distant from Israeli Arabs. FMF is probably rare among the Israeli Bedouins, since we have encountered only two Bedouin families suffering from FMF, in a tertiary rheumatic disease clinic serving a population of 100,000 Bedouins.

MEFV mutation analysis was performed on two Bedouin families, comprising 18 individuals, 6 of which suffered from FMF. Both families carried mutations M694I and V726A, and one of them carried mutation E148Q. These mutations have been described in Arab FMF families from the Maghreb [Bernot et al., 1998; French Consortium, 1997] and are also found Israeli Arabs [Brik et al., 1999]. Of the three mutations, M694I (Ara-2) is common in Arabs and is rarely encountered among our Jewish patients. The V726A mutation is widely distributed in the Mediterranean basin, but rare in the Jewish North African community [French Consortium, 1997; International Consortium, 1997]. Mutation E148Q is found in all ethnic groups suffering from FMF [Bernot et al., 1998; Samuels et al., 1998]. The rarity of FMF among Bedouins on the one hand and sharing common mutations between Bedouins and Arabs in particular mutations M694I on the other hand, may suggest that the mutated FMF genes may have been acquired from neighboring Arab tribes and villages.

Variability in the severity of FMF has been related to the ethnicity of patients [Pras et al., 1998], and to specific *MEFV* mutations prevalent in these ethnic groups [Pras et al., 1997]. The scoring of disease severity in relation to genotype in the Bedouin patients shows a moderate disease for three patients carrying the M694I/V726A genotype and a mild disease for one patient carrying the M694I/E148Q genotype and one patient carrying the M694I/V726A genotype. One child

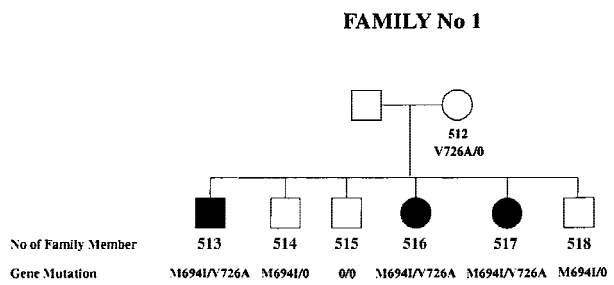

Fig. 2. Distribution of *MEFV* mutations in family 1.

Table I. Score of FMF Severity in Bedouin Patients

No. of patients	Genotype	Age at onset	Frequency of attacks	Colchicine dose	Arthritis	Erysipelas-like rash	Amyloidosis (yes/no)	Total
502	M694I\V726A	2	1	2	2	0	0	7
504	M694I\E148Q	0	1	2	0	0	0	3
509	M694I\V726A	1	2	0	2	0	0	5
513	E148Q/O	1	1	1	0	0	0	3
516	M694I/V726A	2	0	1	0	0	0	3
517	M694I/V726A	2	1	1	2	0	0	5

with the M694I/V726A genotype, who has no FMF at present, is further indication of the decreased severity of this genotype. A larger group of patients with these genotypes needs to be assessed to establish the correlation with disease severity. The genotype-phenotype studies are of special interest in Bedouins, who have low incidence of FMF and lead a unique nomadic life. They may prove instrumental in analysis of the role of environmental factors in the course and severity of FMF compared with Arabs conducting different life styles. In particular, it is important to study mutation M694I with disease outcome, since M694V, a different mutation that occurs in the same amino acid, is associated in homozygotes with increased risk for developing amyloidosis [Livneh et al., 1999] and severe disease manifestations.

In one Bedouin FMF patient only one maternal *MEFV* mutation has been found. However, six other children who carry one maternal mutation are healthy, indicating that the parental chromosome they share does not carry an additional *MEFV* mutation. Therefore, E148Q is the sole mutation in *MEFV* in this patient. Indeed, a complete sequence of the code region of this patient and the father revealed no other mutations. The occurrence of FMF in heterozygotes has been previously reported [Samuels et al., 1998] and is still not understood.

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